REMARKS

Claims 4-15 have been amended to clarify the source of the submucosa is vertebrate stomach tissue. Claims 16-20 have been added. Support for new claim 16 is found throughout the specification, including for example, at page 8 lines 25-27. New claims 17-20 are directed to embodiments wherein a growth modifier compound is added to the cell culture growth substrate. Support for that amendment is found throughout the specification, including for example, at page 8, line 34 through page 9, line 9.

Rejection of Claims 4-15 for Obviousness

Claims 4-15 stand rejected under 35 USC 103 as being as being obvious over WO 96/24661 and/or U.S. Patent No. 5,695,998 (the '998 patent) taken with Gottrup et al., U.S. Patent No. 5,759,830 (the '830 patent), and U.S. Patent No. 4,829,000 (the '000 patent). Applicants respectfully traverse the Examiner's rejection.

As noted previously, all of the rejected claims (i.e., claims 4-15) require a step of contacting "cells *in vitro* with a cell growth substrate ... comprising submucosa from stomach tissue of a warm blooded vertebrate." None of the cited references, alone or in combination, mentions or suggests using stomach submucosal tissue as a cell growth substrate. In fact, the word "stomach" does not appear in any of the cited references (WO 96/24661, the '998 patent, the '830 patent, or the '000 patent) except Gottrup et al. The only description of stomach tissue in Gottrup et al. is a disclosure that stomach tissue comprises collagen.

Applicants concede that intestinal submucosa and stomach submucosa each contain collagen, but respectfully submit that this one commonality between the two distinct materials fails to provide motivation to one of ordinary skill in the art, at the time of the present invention, to use submucosa derived from stomach tissue in a similar manner as previously described for submucosa derived from intestinal tissue. First of all, as described in the prior art, intestinal submucosa was found to have surprising activities as a remodeling tissue graft and as a cell culture substrate. See US patents 4,902,508, 5,866,414 and 5,695,998, for example. These unique properties of intestinal submucosa tissue to remodel upon implantation *in vivo*, and to support the proliferation and growth, and/or differentiation of cells cultured *in vitro*, are believed to result from the unique, natural microstructure of the collagen based matrix, and are not merely due to the presence of collagen in the material.

Intestinal submucosa is a complex tissue that in addition to collagen, includes growth factors, glycoproteins, proteoglycans, and glycosaminoglycans in their natural configuration and natural concentration. The discovery of the remodeling and enhanced cell culture capabilities of intestinal submucosa was surprising, and at the time, thought to be unique to intestinal submucosa. Thus the knowledge that other naturally occurring materials exist that contain collagen would simply not be sufficient by itself to convince one of ordinary skill in the art that such a collagen bearing material would also demonstrate the surprising activities of intestinal submucosa tissue. In this regard applicants note that collagen is the most abundant protein in mammals, making up about 25% of the total protein content. Applicants respectfully submit that the mere disclosure of the presence of such a ubiquitous protein in a material cannot provide the sole rationale for identifying materials that will "obviously" exhibit the same surprising and unexpected properties that intestinal submucosa tissue exhibits.

The Examiner's observation that both materials share a common component (collagen) is simply insufficient information to provide any reasonable expectation to one of ordinary skill in the art that the two materials would perform similarly. Furthermore, the Examiner's generic statement regarding the fact that both materials contain collagen is overly simplistic. Extracellular matrices do not simply contain one form of collagen but rather contain multiple forms of collagen (e.g., twenty eight different types of collagen have been characterized) wherein the ratio and density of the collagen fibers (e.g., type I-collagen vs. type III collagen) has an impact on the response of cells to the material. Furthermore, as mentioned above, additional natural components of the matrix (e.g., growth factors, glycoproteins, proteoglycans, and glycosaminoglycans) also substantially impact the response of cells to the material. Accordingly, one of ordinary skill in the art, at the time the invention was made, would have no reasonable expectation of success that a material derived from a different organ (the stomach) could in fact substitute for intestinal submucosa tissue.

As further evidence of applicants' position, applicants note that the US Patent and Trademark Office has determined that stomach submucosa is a material that is patentably distinct from intestinal submucosa. In particular, applicants note that US patent no. 6,099,567 (with composition claims directed to stomach submucosa) issued in light of prior art describing the preparation of intestinal submucosa (see US patent nos. 4,902,508 and 5,281,422). Thus as indicated by the issuance of the '567 patent, intestinal submucosa and stomach submucosa are

patentably distinct materials, and at the time of the present invention there was no reasonable expectation that submucosa from vertebrate stomach tissue would exhibit the beneficial properties that are exhibit by submucosa from vertebrate small intestines, such that one could substitute for the other.

As noted in the present application stomach submucosa has been found to exhibit unexpected properties. In particular, as described in Example 4, stomach submucosa substrates were capable of supporting the growth of *H. pylori*, a bacterial strain that has been very difficult to culture *in vitro*. The Examiner has failed to cite an objective rationale for why one of ordinary skill at the time this invention was made, working in this unpredictable field, would believe that stomach submucosa could be used as a cell culture substrate that exhibits such beneficial properties.

Many natural animal tissues contain collagen and this fact alone cannot provide a reasonable expectation that all such materials could be used as a substitute for intenstinal submucosa tissue. Applicants were the first to discover that stomach submucosa exhibits unexpected properties in its use as a tissue graft material and as a cell culture substrate. Absent applicants' discovery there was no reasonable expectation that the material would function in this manner. Accordingly, applicants respectfully submit the Examiner has failed to meet her burden in establishing a *prima facie* case of obviousness and applicants respectfully request the withdrawal of the rejection of claims 4-15 under 35 U.S.C. § 103(a).

Rejection of Claims 4-15 for Obviousness-Type Double Patenting

The Examiner has rejected claims 4-15 for obviousness-type double patenting as being unpatentable over claim 1 of US Patent No. 5,695,998. Applicants respectfully traverse this rejection.

As noted in the preceding section, stomach submucosa is a patentably distinct material over the intestinal submucosa tissue described in US Patent No. 5,695,998. The arguments discussed above with regards to the rejection of the claims under 35 USC 103 apply with equally force to the obviousness-type double patenting rejection. Accordingly, applicants respectfully submit claims 4-15 in the instant application are not obvious over claim 1 of the '998 patent because a new submucosa tissue (i.e., stomach submucosa tissue) is specified in the claims of the

instant application. Withdrawal of the rejection of claims 4-15 for obviousness-type double patenting is respectfully requested.

Applicants believe that the present application is now in condition for allowance and such action is respectfully requested. If the Examiner has any questions or comments such that a conversation would speed prosecution of this application, the Examiner is invited to call the undersigned at (434) 220-2866.

Respectfully submitted,

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